Author’s response to reviews

Title: Phenobarbital versus Morphine in the management of Neonatal Abstinence Syndrome, a randomized control trial

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Version: 5
Date: 23 October 2014

Author’s response to reviews: see over
Dear Sir/Madam

Thank you most sincerely for your kind consideration of our paper entitled "Phenobarbital versus Morphine in the management of Neonatal Abstinence Syndrome, a randomized control trial" with the manuscript number of "MS: 9986270081386787". Here I am submitting the changes made to the manuscript according to the precious comments of the reviewers and also the revised version of the paper. We hope they are to your satisfaction and that of the reviewers.

These changes were made to the manuscript:

1. In the introduction section, in the lines 70 – 73, this sentence was added "The treatment rate is usually higher among poly substance and opioid dependent mothers (typically 60-70%) and lower in stimulants only exposed neonates (less than 10%) whose the majority do not require pharmacologic treatment."

2. Two references (Fulroth R 1989 and Smith L 2003) regarding the treatment of stimulants only exposed neonates were added to the manuscript (references 6,7) as requested.

3. The references and the reference list were rearranged given the changes made.

4. In the introduction section, line 105, as requested the sentence was changed as follows: "in the neonates born to drug (opioids, stimulants and polysubstance) dependent mothers who exhibit signs of NAS requiring pharmacologic treatment."

5. The following sentences were added to the limitations of the study as requested, in the lines 278 - 281: "To minimize the factors that could potentially bias the results of the study, many exclusion criteria were used, therefore the generalizability of the findings should be considered when interpreting the results of this study."
6. In the whole manuscript "Crack" was changed to "Cocaine".

7. The first words of the sentences were capitalized.

The answers to the reviewers' comments:

1. As we mentioned in the manuscript and also in our previous comments to the reviewers, in the available literature, including the huge literature reviews and Cochrane review that were cited in our manuscript, no loading dose of Phenobarbital was used, therefore in the published studies it is still unknown if there is any differences in the duration of treatment and hospital stay in the Morphine versus Phenobarbital treated groups when loading dose of Phenobarbital is used. In addition in our study this treatment was conducted on opioids, stimulants and polysubstance exposed neonates, this was also a unique approach which was not undertaken in the available published studies and reviews. Given the results of this study and its target population and the used treatments, more similar studies are required to reveal more aspects of this complicated problem and its treatment options.

2. Unfortunately in our study we do not have exact numbers and percentage of the infants who had NAS but did not require pharmacologic treatment; because these infants were not eligible to be included in the study and did not enter the study from the first.

3. In the manuscript in the Method – Study population and study design section, in the line 118, it is already stated that maternal drug use was considered based on urine toxicology.

4. The tables 1 and 2, had been added for easier and better understanding of the used protocols, as was recommended by the reviewers and the statisticians.
Again I would like to thank you most sincerely for your precious comments; they were very helpful and helped us a lot in enhancing the quality of the paper.

Yours Sincerely

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